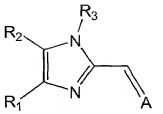
What is claimed is:

1. A compound of Formula I



Formula I

wherein:

R_1 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);

R_2 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl and halogen);

R_3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, arylC_{1-5}alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl)), heteroarylC_{1-5}alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC_{1-5}alkyl, diaminoC_{1-5}alkyl, phthalimidoC_{1-5}alkyl, succinimidoC_{1-5}alkyl, SEM, C_{1-5}alkylcarbonyl, C_{1-5}alkylcarbonylC_{1-5}alkyl, C_{1-5}alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC_{1-5}alkyloxycarbonyl and aryloxycarbonylC_{1-5}alkyl;

A is a five to seven member heterocyclyl ring optionally substituted with one to

two substituents independently selected from X; wherein the ring has an unsaturated bond of attachment at a ring carbon atom; has a ring nitrogen atom substituted with a substituent selected from W adjacent to the ring carbon of attachment; has a ring carbon atom adjacent to the ring carbon of attachment; optionally has 1 or 2 double bonds formed in the ring between adjacent ring members; and, optionally has 1 or 2 ring members independently selected from the group consisting of O, N and S;

W is a substituent selected from the group consisting of hydrogen, C_{1-5}alkyl, C_{1-5}alkoxy, aminoC_{1-5}alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl), arylC_{1-5}alkyl and heteroarylC_{1-5}alkyl (wherein the aryl, heteroaryl and C_{1-5}alkyl portions of any of the foregoing substituents are optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl) and nitrile); and,

X is a substituent selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkenyl, C_{1-5}alkynyl, C_{1-5}alkoxy, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl), aminoC_{1-5}alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl), aryl, arylC_{1-5}alkyl, heteroaryl and heteroarylC_{1-5}alkyl (wherein the aryl, heteroaryl and C_{1-5}alkyl portions of any of the foregoing substituents are optionally substituted with one to two substituents independently selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl) and nitrile);

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 wherein R_1 is phenyl (optionally substituted with

one to five substituents independently selected from the group consisting of C_{1-5}alkyl and halogen).

3. A compound of claim 2 wherein R_1 is phenyl substituted with a substituent selected from halogen.

4. A compound of claim 3 wherein R_1 is phenyl substituted with fluorine.

5. A compound of claim 1 wherein R_2 is heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl and halogen).

6. A compound of claim 5 wherein R_2 is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 4-pyrrolinyl, 5-pyrrolinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-imidazolinyl, 4-imidazolinyl, 5-imidazolinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 4-1,2,3-oxadiazolyl, 5-1,2,3-oxadiazolyl, 4-1,2,3-triazolyl, 5-1,2,3-triazolyl, 2-1,3,4-thiadiazolyl, 5-1,3,4-thiadiazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl and 2-1,3,5-triazinyl optionally substituted with one substituent selected from C_{1-5}alkyl.

7. A compound of claim 6 wherein R_2 is selected from the group consisting of 4-pyridinyl, 4-pyrimidinyl and (2-butyl)pyridin-4-yl.

8. A compound of claim 1 wherein R_3 is selected from the group consisting of hydrogen, C_{1-5}alkyl and arylC_{1-5}alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, halogen and amino (wherein

amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl)).

9. A compound of claim 8 wherein R_3 is selected from the group consisting of hydrogen and phenylC_{1-5}alkyl (wherein phenyl is optionally substituted with one substituent selected from C_{1-5}alkoxy).

10. A compound of claim 9 wherein R_3 is selected from the group consisting of benzyl, phenethyl and phenylpropyl.

11. A compound of claim 1 wherein A is selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, hexahydro-1*H*-azepine, hexahydro-1*H*-1,3-diazepine, hexahydro-1,3-oxazepine, hexahydro-1,3-thiazepine and hexahydro-1*H*-1,3,5-triazepine.

12. A compound of claim 11 wherein A is selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl and piperazinyl.

13. A compound of claim 1 wherein W is a substituent selected from the group consisting of hydrogen, C_{1-5}alkyl and C_{1-5}alkoxy (wherein C_{1-5}alkyl for any of the foregoing substituents is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl) and nitrile).

14. A compound of claim 13 wherein W is a substituent selected from the group consisting of hydrogen and C_{1-5}alkyl.

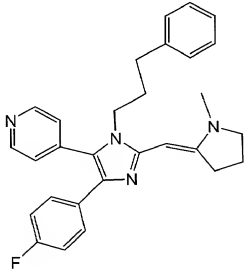
15. A compound of claim 14 wherein W is a substituent selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl and *t*-butyl.

16. A compound of claim 1 wherein X is a substituent selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkenyl, C_{1-5}alkynyl, C_{1-5}alkoxy and amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl).

17. A compound of claim 16 wherein X is a substituent selected from C_{1-5}alkyl.

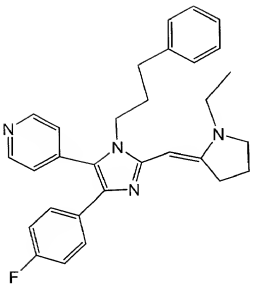
18. A compound of claim 17 wherein X is a substituent selected from the group consisting of methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl and *t*-butyl.

19. A compound of claim 1 selected from



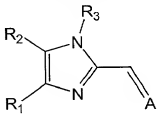
and pharmaceutically acceptable salts thereof.

20. A compound of claim 1 selected from



and pharmaceutically acceptable salts thereof.

21. A method for preparing a compound of Formula I



Formula I

wherein

R_1 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);

R_2 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl and halogen);

R_3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, arylC_{1-5}alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl)), heteroarylC_{1-5}alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC_{1-5}alkyl, diaminoC_{1-5}alkyl, phthalimidoC_{1-5}alkyl, succinimidoC_{1-5}alkyl, SEM, C_{1-5}alkylcarbonyl, C_{1-5}alkylcarbonylC_{1-5}alkyl, C_{1-5}alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC_{1-5}alkyloxycarbonyl and aryloxycarbonylC_{1-5}alkyl;

A is a five to seven member heterocyclyl ring optionally substituted with one to two substituents independently selected from X; wherein the ring has an unsaturated bond of attachment at a ring carbon atom; has a ring nitrogen atom substituted with a substituent selected from W adjacent to the ring carbon of attachment; has a ring carbon atom adjacent to the ring carbon of attachment; optionally has 1 or 2 double bonds formed in the ring between adjacent ring members; and, optionally has 1 or 2 ring members independently selected from the group consisting of O, N and S;

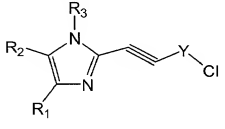
W is a substituent selected from the group consisting of hydrogen, C_{1-5}alkyl, C_{1-5}alkoxy, aminoC_{1-5}alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl), arylC_{1-5}alkyl and heteroarylC_{1-5}alkyl (wherein the aryl, heteroaryl and C_{1-5}alkyl portions of any of the foregoing substituents are optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl) and nitrile);

X is a substituent selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkenyl, C_{1-5}alkynyl, C_{1-5}alkoxy, amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl),

aminoC$_{1-5}$alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C$_{1-5}$alkyl), aryl, arylC$_{1-5}$alkyl, heteroaryl and heteroarylC$_{1-5}$alkyl (wherein the aryl, heteroaryl and C$_{1-5}$alkyl portions of any of the foregoing substituents are optionally substituted with one to two substituents independently selected from the group consisting of halogen, C$_{1-5}$alkyl, C$_{1-5}$alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C$_{1-5}$alkyl) and nitrile);

and pharmaceutically acceptable salts thereof; comprising,

converting an intermediate compound of Formula II



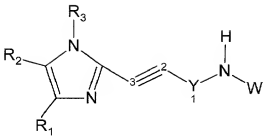
Formula II

wherein

Y is a three to five member linear alkylene, alkenylene, heteroalkylene or heteroalkenylene chain optionally substituted with one to two substituents independently selected from X; wherein the alkenylene and heteroalkenylene chain has 1 or 2 double bonds formed in the chain between adjacent members; and, wherein the heteroalkylene and heteroalkenylene chain has 1 or 2 members independently selected from the group consisting of O, N and S; and,

all other substituents are as previously defined;

by ammonolysis, using an excess of a compound selected from $H_2N(W)$ in an appropriate solvent, to form a secondary amine intermediate of Formula III; and,



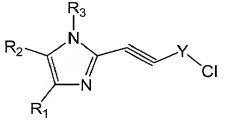
Formula III

coupling the amine at the 2 position of the triple bond by a Michael addition, in the presence of appropriate reagents and solvents, to form the compound of Formula I.

22. The method of claim 21 wherein Y is a three to five member linear alkylene chain optionally substituted with one to two substituents independently selected from X.

23. The method of claim 22 wherein Y is an unsubstituted three to five member linear alkylene chain.

24. An intermediate compound of Formula II



Formula III

wherein

R_1 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);

R_2 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5}alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein

heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl and halogen);

R_3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, arylC_{1-5}alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5}alkyl, C_{1-5}alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C_{1-5}alkyl)), heteroarylC_{1-5}alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC_{1-5}alkyl, diaminoC_{1-5}alkyl, phthalimidoC_{1-5}alkyl, succinimidoC_{1-5}alkyl, SEM, C_{1-5}alkylcarbonyl, C_{1-5}alkylcarbonylC_{1-5}alkyl, C_{1-5}alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC_{1-5}alkyloxycarbonyl and aryloxycarbonylC_{1-5}alkyl; and,

Y is a three to five member linear alkylene, alkenylene, heteroalkylene or heteroalkenylene chain optionally substituted with one to two substituents independently selected from X; wherein the alkenylene and heteroalkenylene chain has 1 or 2 double bonds formed in the chain between adjacent members; and, wherein the heteroalkylene and heteroalkenylene chain has 1 or 2 members independently selected from the group consisting of O, N and S;

with the proviso that Y cannot be selected from $(CH_2)_3$;

and pharmaceutically acceptable salts thereof.

25. The compound of claim 24 wherein Y is a four to five member linear alkylene chain optionally substituted with one to two substituents independently selected from X.

26. The method of claim 25 wherein Y is an unsubstituted three to five member linear alkylene chain.

27. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.

28. A pharmaceutical composition comprising a compound according to claim 19 and a pharmaceutically acceptable carrier or diluent.

29. A pharmaceutical composition comprising a compound according to claim 20 and a pharmaceutically acceptable carrier or diluent.

30. A method for treating a cytokine related disease comprising administering a compound of claim 1 to a mammal at an effective dose.

31. A method for treating a cytokine related disease comprising administering a pharmaceutical composition of claim 27 to a mammal at an effective dose.

32. The method of claim 30 wherein the compound of claim 1 is administered orally and the effective dose is from about 0.1 mg/kg/day to about 100 mg/kg/day.

33. The method of claim 32 wherein the effective dose is from about 0.1 mg/kg/day to about 50 mg/kg/day.

34. The method of claim 30 wherein the cytokine related disease is arthritis.

35. The method of claim 34 wherein the compound of claim 1 is administered orally and the effective dose is from about 0.1 mg/kg/day to about 100 mg/kg/day.

36. The method of claim 35 wherein the effective dose is from about 0.1 mg/kg/day to about 50 mg/kg/day.